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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,128	02/20/2004	James McSwiggen	MBHB04-105 (400.146)	2611

20306 7590 08/10/2005

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
CHONG, KIMBERLY	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/783,128	MCSWIGGEN, JAMES	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07/14/05, 03/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IDS 11/15/04*.

5.0-3

DETAILED ACTION

Status of the Application

Claims 1-31 are currently pending and under examination.

Priority

In the instant case, the priority date granted is 02/20/2004, the filing date of the instant application. The instant application 10/783,128 does not receive the benefit of the earlier filing date of the prior applications as listed on page 1 of the specification because claims 1-31 of the instant application are not supported by the specification and claims of the previously mentioned provisional applications. The instant application 10/783,128 disclose a siNA molecule that directs cleavage of a huntingtin (HD) RNA via RNA interference. Although the prior applications disclose siNA molecules, the disclosures of the prior application fail to discuss a siNA molecule that directs cleavage of a huntingtin (HD) RNA via RNA interference. If Applicant believes the prior applications provide support then applicant must point with particularity to where such support can be found in the specifications of the prior applications.

Thus, the instant application 10/783,128 has a priority date of 02/20/2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-15, 18 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 recites the limitation "wherein pyrimidine nucleotides". There is insufficient antecedent basis for this limitation in the claim.

Claim 14 recites the limitation "wherein purine nucleotides". There is insufficient antecedent basis for this limitation in the claim.

Claim 15 recites the limitation "wherein pyrimidine nucleotides". There is insufficient antecedent basis for this limitation in the claim.

Claim 18 recites the limitation "wherein pyrimidine nucleotides". There is insufficient antecedent basis for this limitation in the claim.

Claim 30 recites the limitation "wherein the 5'-end of the fragment". There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-31 broadly reads on any double stranded short interfering nucleic acid (siNA) molecule that directs cleavage of any Huntingtin (HD) RNA via RNA interference, wherein each strand of said siNA molecule is 19 to 23 nucleotides in length; and the siNA strand comprises a

nucleotide sequence that is complementary to a nucleotide sequence of said HD RNA and the sense strand is complementary to the antisense strand; and further the siNA molecule comprises one or more chemically modified nucleotides.

Although the specification as filed discloses siNA sequences targeted to HD (see Tables III and IV), the specification does not provide information regarding what structure directs cleavage of any HD RNA via RNAi. The scope of the claimed invention is so broad that the skilled artisan would not be able to envisage the entire genus claimed of siNA molecules that would direct cleavage of any HD RNA and further the skilled artisan would recognize that the applicant was in possession of the claimed invention at the time of filing.

Further, there is no structure found in the specification or known in the art that relates to the structure of a siNA that directs cleavage of any HD gene for any species or directs cleavage of any isoforms or variants of any HD gene. Moreover, the ability for a specific siNA to direct cleavage of a target RNA via RNAi must be experimentally determined and cannot be predicted.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g.,

Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")

Thus, the instantly claimed invention cannot be said to have been adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filling date sought, applicant was in possession of the claimed invention because the specification, while providing information on siNA sequences targeted to HD RNA, does not provide any other information or guidance as to what siNA sequence for which HD RNA will broadly provide cleavage via RNAi.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 13-14, 19-20 and 23-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden et al. (US 2002/0187931), Hammond et al. (Nature 2001), Elbashir et al. (EMBO Journal, 2001) and in further view of Parrish et al. (Molecular Cell, 2000).

Claim 1 is drawn to a double-stranded siNA molecule molecule that directs cleavage of a HD RNA via RNA interference wherein each strand is about 19 to 23 nucleotides in length and one strand is complementary to the HD RNA and further at least one strand in chemically modified. Claims 2-9 and 27-30 recite the siNA comprises no ribonucleotides or comprises ribonucleotides, one strand of the siNA is complementary to the HD gene or at least has 19 nucleotides that are complementary and the other strand is substantially similar to the HD gene. Claims 10-12 recite the siNA has a polynucleotide linker or a non-polynucleotide linker. Claims 13-26 recite chemical modifications to the nucleotide. Claim 31 recites a pharmaceutical composition comprising a siNA.

Hayden et al. teach an antisense compound targeted to a HD gene (see paragraph 0082). Hayden et al. further teach the antisense compound can be between 15-30 nucleotides in length and the antisense compound can be modified to increase the biological stability (see paragraph 0087). Hayden et al. do not teach a double-stranded nucleic acid molecule targeted to a HD gene and further do not teach the nucleotides of the double-strands can be modified.

Hammond et al. teach two methods for silencing specific genes: antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from "...questionable specificity and incomplete efficacy." (see page 110, column 1). Hammond et al. further teach ..."dsRNAs have been shown to inhibit gene expression in a sequence-specific manner" and

further "RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression." Hammond et al. do not teach double-stranded nucleic acid comprising common nucleotide modifications.

Elbashir et al. teach siRNA molecules which are 21 nucleotides in length and wherein 19 nucleotides of the sense strand are complementary to the antisense strand (Figure 5). Elbashir et al. further teach substitutions on either strand by 2'deoxy residues or 2'-O-methyl residues and further teach at least two 3' terminal nucleotides which are not base-paired to the nucleotides of the other strand (see Figure 4). Elbashir et al. teach a 5'-phosphate on the antisense strand (see page 6886) and teach delivery of double-stranded molecules in buffer (i.e. water) which is considered to be a pharmaceutically acceptable carrier or diluent (see materials and methods).

Parrish et al. teach a siRNA with an antisense or sense region comprising 2'-deoxy-2'-fluoro pyrimidine nucleotides (see Figure 5).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a dsRNA targeted to a HD gene, at taught by Hayden et al. and further it would have been obvious for one of ordinary skill in the art to make a dsRNA which are 21 nucleotides in length with chemical modifications, as taught by Elbashir et al. and Parrish et al.

One would have been motivated to use a dsRNA targeted to a HD gene instead of an antisense because Hammond et al. teach using dsRNA to inhibit gene expression is more sequence specific than using antisense methodologies and RNAi using dsRNA is a more potent method requiring only a few molecules of dsRNA per cell. Further, Elbashir et al. and Parrish et al. provide motivation to make a dsRNA 21 nucleotides in length with chemical modifications

because the length of the nucleotide and the modifications are important for mediating RNA interference.

Finally, one would have a reasonable expectation of success because Hayden et al. teach antisense molecules can be targeted to a HD gene and regulate gene expression, Hammond et al. teach that of the two methods used for silencing gene function, RNAi using dsRNA is more potent and sequence specific than antisense and finally Elbashir et al. and Parrish et al. teach making a dsRNA 21 nucleotides in length with chemical modifications is important for mediating RNAi.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-9, 13-14, 16-17, 19-20 and 22-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden et al, Hammond et al., Elbashir et al. (EMBO Journal 2001) as applied to claims 1-9, 13-14, 16-17, 19-20 and 22-31 above and in further view of Matulic-Adamic et al. (U.S. Patent No. 5,998,203)

The teachings of Hayden et al., Hammond et al. and Elbashir et al. are relied upon for the reasons described above in the previous 103 rejection. They do not teach terminal cap moieties at the 5' and/or 3' end of the sense region.

Matulic-Adamic et al. et al. teach terminal cap moieties at the 5' and/or 3' end of the antisense or sense region of a double stranded nucleic acid. The term "siNA" is defined in the instant specification as any nucleic acid molecule capable of inhibiting or down regulating gene expression, for example by mediating RNA interference in a sequence specific manner. Matulic-

Adamic et al. teach double stranded short interfering nucleic acids that are targeted to any gene and therefore can mediate RNAi.

The teachings of Hayden et al., Hammond et al. and Elbashir et al. are obvious for the reasons outlined above. It would have been further obvious to one of ordinary skill in the art at the time the inventions was made to modify a double stranded nucleic acid with a terminal cap moiety to increase nuclease resistance. One would have been motivated to modify a double stranded nucleic acid because Matulic-Adamic et al. teach incorporation of terminal cap moieties protect the nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid as well as facilitates the uptake of the nucleic acid molecules (see column 2). One of ordinary skill in the art would have a reasonable expectation of success of incorporating terminal cap moieties into double stranded nucleic acid molecules because Matulic-Adamic et al. teach the stability of modified double stranded nucleic acid molecules (see Example 3).

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-14, 19-20, 22 and 23-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden et al, Hammond et al., Elbashir et al. (EMBO Journal, 2001) as applied to claims above and in further view of Schmidt et al. (Nucleic Acids Research, 1996) and Kennerdell et al. (Nature Biotechnology, 2000).

The teachings of Hayden et al., Hammond et al. and Elbashir et al. are relied upon for the reasons described above in the previous 103 rejection. They do not teach use of hairpin RNAs as

siRNAs and further do not teach the sense and the antisense regions are connected via a linker that is a polynucleotide or non-polynucleotide.

Kennerdell et al. teach hairpin RNA molecules that can mediate RNA interference and teach the results are similar to the results using dsRNA and therefore applicable in RNAi interference methodologies (see page 896). Kennerdell et al. do not teach the sense and the antisense regions are connected via a linker that is a polynucleotide or non-polynucleotide.

Schmidt et al. teach a hairpin RNA comprising a sense and an antisense region connected via a linker that is a polynucleotide or non-polynucleotide (see Figure 3). Schmidt et al. teach the linkers increase hairpin RNA cleavage efficiencies (see page 575).

The teachings of Hayden et al., Hammond et al. and Elbashir et al. are obvious for the reasons outlined above. It would have been further obvious to one of ordinary skill in the art at the time the inventions was made to use hairpin RNA for RNA interference and to modify the hairpin RNA, as taught by Schmidt et al., to increase the cleavage efficiency. One would have been motivated to use hairpin RNA because Kennerdell et al. teach efficient RNA interference using hairpin RNA. One of ordinary skill in the art would have a reasonable expectation of success in using hairpin RNA because Kennerdell et al. teach that RNA interference can be mediated by hairpin RNA.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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Kimberly Chong
Examiner
Art Unit 1635